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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/763,037	01/22/2004	Robert J. Schwartz	HO-P02659US1	8488

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FULBRIGHT & JAWORSKI, LLP
1301 MCKINNEY
SUITE 5100
HOUSTON, TX 77010-3095

EXAMINER	
LONG, SCOTT	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/763,037	SCHWARTZ ET AL.	
	Examiner	Art Unit	
	SCOTT LONG	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,6 and 8-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,6 and 8-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/18/2008 has been entered.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b).

Claim Status

Claim 8 is amended. Claims 1-4, 7, and 16-41 are cancelled. Claims 5-6 and 8-15 are under current examination.

Priority

This application claims benefit from provisional U.S. Application No. 60/441,668 (filed 01/22/2003). The instant application has been granted the benefit date, 22 January 2003, from the application 60/441,668.

Response to Arguments - Claim Rejections 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 5-6 and 8-15 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Drewett et al. (Journal of Biological Chemistry. 2001. Vol.276; No.36: 33444-33451) in view of Narula et al. (PNAS. July 1999. Col.96: 8144-8149) for the reasons of record.

Applicant's arguments (Remarks, pages 4-6, filed 8/18/2008) have been fully considered but are not persuasive. Applicants traverse the instant rejection on the following grounds:

The applicant asserts the examiner has not established a case of *prima facie* obviousness because he has used impermissible hindsight reasoning. In particular, the applicant asserts that absent the examiner's use of hindsight reasoning, "there would be no basis for combining the elements from these separate references [Drewett et al. and Narula et al.] to arrive at the claimed material" (Remarks, page 4, lines 25-26).

Contrary to the applicant's assertion, the examiner provided a reasoned explanation of why a skilled artisan would have combined the teachings of Drewett and Narula. The examiner suggests that in light of the recent KSR decision, a necessity for a "reason or suggestion" is no longer required. KSR forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. See the recent Board decision Ex parte Smith, --USPQ2d, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396). This reasoning follows: Taken together, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to combine the teachings of Drewett et al. with Narula et al. to develop a method of diagnosing cardiac disease in an individual comprising the step of identifying cleavage of SRF in at least one cell from a sample from said individual. The person of ordinary skill in the art would have been motivated to make those modifications because both references indicate a link between apoptosis and disease states. Narula et al. indicate the relationship between apoptosis and heart failure, while Drewett et al. describe the relationship between Serum Response Factor (SRF) cleavage and apoptosis. All of the details of the claimed invention are taught by the references, including immunoblotting with antibodies specific

for N- or C-termini of SRF and comparisons of normal cardiac tissue and tissue from patients with end-stage cardiac failure. The skilled artisan would have had a reasonable expectation of success in combining the teachings of Drewett et al. and Narula et al. because the methods and reagents are well characterized and commercially available. Furthermore, both references adequately explain the relationship of apoptosis to disease and methodologies used in their biochemical analyses. Therefore the examiner finds the applicant's argument unpersuasive.

Additionally, the applicant asserts that the "references do not teach the measurement of cleaved SRF, and particularly measurement of an N-terminal or C-terminal region of SRF or SEQ ID NO:5. Contrary to the applicant's assertion, Drewett et al. teach measurement of both C- and N-terminal regions of SRF (page 33445, Results). SEQ ID NO:5 is a portion of the N-terminal region of SRF (Specification, parag.0010). Antibodies immunogenic against SEQ ID NO:5 are directed to the N-terminus of SRF. This would be obvious over the teachings of the cited references. The examiner finds this argument unpersuasive.

Finally, the applicant asserts that the instant application provides "unexpected results." The examiner admits to being unable to determine from the applicant's remarks (page 6, parag.2), exactly what results are unexpected in the claimed method. Diagnosing diseases by methods comprising immunoblotting for aberrant proteins is common to many diagnostic tests. The examiner had previously described why the teachings of Drewett and Narula would lead a skilled artisan to immunoblot for aberrantly cleaved SRF. The applicant seems to base their claim of unexpected results

upon their own reading of the state of the art and not on a factual basis of some unexpected result produced by the diagnostic method (e.g., as if 1+1 were greater than 2). If there is some "unexpected result," the examiner requests factually supported objective evidence to justify this assertion and further requests that the applicant more clearly explain what feature of the instant claims provided the "unexpected results." Therefore, the examiner finds this argument unpersuasive.

Therefore, the examiner hereby maintains the rejection of claims 5-6 and 8-15 under 35 U.S.C. 103(a) as being unpatentable over Drewett et al. in view of Narula et al.

The examiner reiterates the pending rejection below:

Claims 5-6 and 8-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Drewett et al. (Journal of Biological Chemistry. 2001. Vol.276; No.36: 33444-33451) in view of Narula et al. (PNAS. July 1999. Col.96: 8144-8149).

Claim 5 is directed to a method of diagnosing cardiac disease in an individual, comprising the step of identifying cleavage of SRF in at least one cell from a sample from said individual.

Claim 6 is directed to the method of claim 5, wherein the sample is from a tissue of the individual.

Claim 8 is directed to the method of claim 5, wherein the cardiac tissue is ventricular tissue.

Claim 9 is directed to the method of claim 5, wherein the identifying step is further defined as comparing levels of cleaved SRF in a sample from an individual suspected of having cardiac failure with a known control reflective of levels of cleaved

SRF in non-failing cardiac tissue, wherein when said sample comprises elevated levels of cleaved SRF compared to said control, said individual suspected of having cardiac failure has a positive diagnosis for cardiac failure.

Claim 10 is directed to the method of claim 9, wherein the identifying step comprises immunoblot analysis for said cleaved SRF.

Claim 11 is directed to the method of claim 10, wherein the immunoblot analysis comprises an antibody against a region of SRF.

Claim 12 is directed to the method of claim 11, wherein the region of SRF is an N-terminal region or a C-terminal region.

Claim 13 is directed to the method of claim 12, wherein the N-terminal region comprises at least a portion of amino acid sequence encoded by the first coding exon of a SRF polynucleotide.

Claim 14 is directed to the method of claim 13, wherein the N-terminal region comprises SEQ ID NO:5.

Claim 15 is directed to the method of claim 5, wherein said cardiac disease is further defined as cardiac failure.

Drewett et al. teach, "these results indicate that SRE-dependent *c-fos* expression is down-regulated early in apoptosis and that…the fragments of SRF generated by caspase cleavage fail to maintain expression levels supported by full-length SRF" (page 33449, col.1) and further teach, "variations in the level of SRF fragments indicated that SRF cleavage might be a regulated event" (page 33445, col.2). Drewett et al. also describe analysis of SRF cleavage products in cells by immunoblotting with antibodies

against the carboxyl- terminus or amino-terminus of SRF (page 33446, Fig.1). Drewett et al. further teach (uncleaved) SRF is required for normal functioning and development of muscle tissue (page 33444, col.2).

Narula et al. teach, "apoptosis has been shown to contribute to loss of cardiomyocytes in cardiomyopathy, progressive decline in the left ventricular function, and congestive heart failure… loss of myocytes contributes to myocardial dysfunction and is a predictor of adverse outcomes in the patients with congestive heart failure, the present demonstration of an activated apoptotic cascade in cardiomyopathy could provide the basis for novel interventional strategies." (page 8144, abstract). Narula et al. further indicate, "protease cleavage…in the myocardial cytoplasmic extracts support the phenomenon of apotosis in end stage heart failure" (page 8148, col.1). Narula et al. teach comparison of biochemical analyses from tissue of normal and cardiac-diseased patients (page 8145, col.1). These patient tissues included ventricular tissue samples.

Taken together, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to combine the teachings of Drewett et al. with Narula et al. to develop a method of diagnosing cardiac disease in an individual comprising the step of identifying cleavage of SRF in at least one cell from a sample from said individual.

The person of ordinary skill in the art would have been motivated to make those modifications because both references indicate an link between apoptosis and disease states. Narula et al. indicate the relationship between apoptosis and heart failure, while Drewett et al. describe the relationship between Serum Response Factor (SRF)

cleavage and apoptosis. All of the details of the claimed invention are taught by the references, including immunoblotting with antibodies specific for N- or C-termini of SRF and comparisons of normal cardiac tissue and tissue from patients with end-stage cardiac failure.

The skilled artisan would have had a reasonable expectation of success in combining the teachings of Drewett et al. and Narula et al. because the methods and reagents are well characterized and commercially available. Furthermore, both references adequately explain the relationship of apoptosis to disease and methodologies used in their biochemical analyses.

Therefore the method as taught by Drewett et al. in view of Narula et al. would have been *prima facie* obvious over the method of the instant application.

Conclusion

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SDL/ Scott Long
Patent Examiner, Art Unit 1633
/Janet L. Epps-Ford/
Primary Examiner, Art Unit 1633